CLAIMS

1. A DNA construct capable of altering the expression of a gene encoding thrombopoietin when inserted by homologous recombination into chromosomal DNA of a cell, said construct comprising:

(a) a targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the thrombopoietin gene;

(b) a regulatory sequence;

(c) an exon; and

(d) an unpaired splice-donor site.

2. The DNA construct of claim 1 wherein the regulatory sequence comprises a promoter.

3. The DNA construct of Claim 2 further comprising a selectable marker gene.

4. The DNA construct of Claim 2 further comprising an amplifiable marker gene.

5. The DNA construct of Claim 1 further comprising a second targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the thrombopoietin gene.

6. The DNA construct of Claim 1 wherein the targeting sequence is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4 or fragments thereof or a sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4 or fragments thereof.

7. The DNA construct of Claim 6 wherein the targeting sequence is a fragment of SEQ ID NO: 3 and is at least about 20 base pairs.

8. The DNA construct of Claim 6 wherein the targeting sequence is a fragment of SEQ ID NO: 4 and is at least about 20 base pairs.

9. The DNA construct of Claim 8 wherein the targeting sequence is at least about 20 base pairs and is a sequence between about nucleotides -1815 to -145, 14 to 245, or 374 to 570 of Figure 5 (SEQ ID NO: 4).

10. An isolated DNA molecule of at least about 20 base pairs selected from the group consisting of SEQ ID NO: 3, a fragment thereof, and a sequence which hybridizes to SEQ ID NO: 3.

11. An isolated DNA molecule of at least about 20 base pairs which is selected from the group consisting of a sequence between about nucleotides -1815 to -145, 14 to 245, or 374 to 570 of Figure 5 (SEQ ID NO: 4), and a sequence which hybridizes to a sequence between about nucleotides -1815 to -145, 14 to 245, or 374 to 570 of Figure 5 (SEQ ID NO: 4).

12. A method of producing a homologously recombinant cell wherein the expression of the thrombopoietin gene is altered, comprising the steps of:

(a) transfecting a cell containing the thrombopoietin gene with the DNA construct of one of Claims 1-9; and

(b) maintaining the transfected cell under conditions appropriate for homologous recombination.

13. A homologously recombinant cell produced by the method of Claim 12.

14. A homologously recombinant cell which expresses thrombopoietin comprising an exogenous regulatory region, an exogenous exon, and an exogenous unpaired splice-donor site operatively linked to an endogenous splice acceptor site of the thrombopoietin gene.

15. The homologously recombinant cell of Claim 14 wherein the exogenous regulatory region, the exogenous exon, and the exogenous unpaired splice-donor site are operatively linked to the endogenous splice acceptor site of the second or third exon of the thrombopoietin gene.

16. A method for producing thrombopoietin comprising the steps of maintaining the homologously recombinant cell of Claim 14 or 15 under conditions appropriate for the production of thrombopoietin.

17. A method for producing thrombopoietin wherein the expression of the thrombopoietin gene is altered, comprising the steps of:

(a) transfecting a cell containing the thrombopoietin gene with the DNA construct of one of Claims 1-9; and

(b) maintaining the transfected cell under conditions appropriate for homologous recombination; and

(c) maintaining the homologously recombinant cell produced in step (b) under conditions appropriate for the production of thrombopoietin.

18. A thrombopoietin produced by the method of Claim 17.

19. A pharmaceutical composition comprising the thrombopoietin of Claim 18.

20. A method of providing thrombopoietin to a mammal in need thereof comprising administering homologously recombinant cells of Claim 14 or 15 in sufficient number to produce a therapeutically effective amount of thrombopoietin in the mammal.

21. A DNA construct capable of altering the expression of a gene encoding DNase I when inserted by homologous recombination into chromosomal DNA of a cell, said construct comprising:

(a) a targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the DNase I gene;

(b) a regulatory sequence;

(c) an exon; and

(d) an unpaired splice-donor site.

22. The DNA construct of claim 21 wherein the regulatory sequence comprises a promoter.

23. The DNA construct of Claim 22 further comprising a selectable marker gene.

24. The DNA construct of Claim 22 further comprising an amplifiable marker gene.

25. The DNA construct of Claim 21 further comprising a second targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the DNase I gene.

26. The DNA construct of Claim 21 wherein the targeting sequence is selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 18 or fragments thereof or a sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 18 or fragments thereof.

27. The DNA construct of Claim 26 wherein the targeting sequence is a fragment of SEQ ID NO: 17 and is at least about 20 base pairs.

28. The DNA construct of Claim 26 wherein the targeting sequence is a fragment of SEQ ID NO: 18 and is at least about 20 base pairs.

29. The DNA construct of Claim 28 wherein the targeting sequence is at least about 20 base pairs and is a sequence between about nucleotides -328 to -2 of Figure 11 (SEQ ID NO: 18).

30. An isolated DNA molecule of at least about 20 base pairs selected from the group consisting of SEQ ID NO: 17, a fragment thereof, and a sequence which hybridizes to SEQ ID NO: 17.

31. An isolated DNA molecule of at least about 20 base pairs which is selected from the group consisting of a sequence between about nucleotides -328 to -2 of Figure 11 (SEQ ID NO: 18) and a sequence which hybridizes to a sequence between about nucleotides -328 to -2 of Figure 11 (SEQ ID NO: 18).

32. A method of producing a homologously recombinant

cell wherein the expression of the DNase I gene is altered, comprising the steps of:

(a) transfecting a cell containing the DNase I gene with the DNA construct of one of Claims 21-29; and

(b) maintaining the transfected cell under conditions appropriate for homologous recombination.

33. A homologously recombinant cell produced by the method of Claim 32.

34. A homologously recombinant cell which expresses DNase I comprising an exogenous regulatory region, an exogenous exon, and an exogenous unpaired splice-donor site operatively linked to an endogenous splice acceptor site of the DNase I gene.

35. The homologously recombinant cell of Claim 34 wherein the exogenous regulatory region, the exogenous exon, and the exogenous unpaired splice-donor site are operatively linked to the endogenous splice acceptor site of the second exon of the DNase I gene.

36. A method for producing DNase I comprising the steps of maintaining the homologously recombinant cell of Claim 34 or 35 under conditions appropriate for the production of DNase I.

37. A method for producing DNase I wherein the expression of the DNase I gene is altered, comprising the steps of:

(a) transfecting a cell containing the DNase I gene with the DNA construct of one of Claims 21-29; and

(b) maintaining the transfected cell under conditions

appropriate for homologous recombination; and

(c) maintaining the homologously recombinant cell produced in step (b) under conditions appropriate for the production of DNase I.

38. A DNase I produced by the method of Claim 37..

39. A pharmaceutical composition comprising the DNase I of Claim 38.

40. A method of providing DNase I to a mammal in need thereof comprising administering homologously recombinant cells of Claim 34 or 35 in sufficient number to produce a therapeutically effective amount of DNase I in the mammal.

41. A DNA construct capable of altering the expression of a gene encoding ß-interferon when inserted by homologous recombination into chromosomal DNA of a cell, said construct comprising:

(a) a targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the ß-interferon gene;

(b) a regulatory sequence;

(c) an exon;

(d) a splice-donor site;

(e) an intron; and

(f) a splice-acceptor site

42. The DNA construct of claim 41 wherein the regulatory sequence comprises a promoter.

43. The DNA construct of Claim 42 further comprising a selectable marker gene.

44. The DNA construct of Claim 42 further comprising an amplifiable marker gene.

45. The DNA construct of Claim 41 further comprising a second targeting sequence comprising DNA which hybridizes to genomic DNA within or upstream of the ß-interferon gene.

46. The DNA construct of Claim 41 wherein the targeting sequence is selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 or fragments thereof or a sequence which hybridizes to a sequence selected from the group consisting of SEQ ID NO: 23, SEQ ID NO: 24 or fragments thereof.

47. The DNA construct of Claim 46 wherein the targeting sequence is a fragment of SEQ ID NO: 23 and is at least about 20 base pairs.

48. The DNA construct of Claim 46 wherein the targeting sequence is a fragment of SEQ ID NO: 24 and is at least about 20 base pairs.

49. An isolated DNA molecule of at least about 20 base pairs selected from the group consisting of SEQ ID NO: 23, a fragment thereof, and a sequence which hybridizes to SEQ ID NO: 23.

50. A method of producing a homologously recombinant cell wherein the expression of the ß-interferon gene is altered, comprising the steps of:

(a) transfecting a cell containing the ß-interferon gene with the DNA construct of one of Claims 41-48; and

(b) maintaining the transfected cell under conditions

appropriate for homologous recombination.

51. A homologously recombinant cell produced by the method of Claim 50.

52. A homologously recombinant cell which expresses ß-interferon comprising an exogenous regulatory region, an exogenous exon, an exogenous splice-donor site, and exogenous intron, and an exogenous splice acceptor site operatively linked to the ß-interferon gene.

53. A method for producing ß-interferon comprising the steps of maintaining the homologously recombinant cell of Claim 52 under conditions appropriate for the production of ß-interferon.

54. A method for producing ß-interferon wherein the expression of the ß-interferon gene is altered, comprising the steps of:

(a) transfecting a cell containing the ß-interferon gene with the DNA construct of one of Claims 41-48; and

(b) maintaining the transfected cell under conditions appropriate for homologous recombination; and

(c) maintaining the homologously recombinant cell produced in step (b) under conditions appropriate for the production of ß-interferon.

55. A ß-interferon produced by the method of Claim 54.

56. A pharmaceutical composition comprising the ß-interferon of Claim 55.

57. A method of providing ß-interferon to a mammal in need thereof comprising administering homologously recombinant cells of Claim 52 in sufficient number to produce a therapeutically effective amount of ß-interferon in the mammal.

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